Table I—Onset and Duration (Time in Minutes) of Buffering Action following Administration of Gastric Antacid Preparations in Human Subjects as Recorded by Heidelberg Capsule Telemetry

Antacid A—Suspension			Antacid B—Suspension			Antacid C—Suspension			Antacid D—Tablet		
Subject	Onset[a]	Duration	Subject	Onset	Duration	Subject	Onset	Duration	Subject	Onset	Duration
1	1	2[d]	1	3	40	1	31	>16	1	2	>46
2	1	13[d]	3	5	24	5	1	12	12[b]	0	0
3[b]	0	0	5	9	8[d]	10[b]	0	0	13	1	6[d]
5	6	12[d]	6	1	11	11	37	>10	15	3	1[d]
6	7	>40	7	2	2[d]	12	2	>40	18	7	2[d]
7[c]	43	> 4	10	3	2[d]	14	7	28			
9	1	10[d]	11	7	8[d]	15[b]	0	0			
10	5	4[d]	12	1	22[d]	16	1	34			
11[b]	0	0				17	27	>20			
12	2	>46				18	25	>22			
13	4	4[d]				19	29	4			
Average onset	3.4(n=8)			3.9(n=8)			17.8(n=9)			3.3(n=4)	

[a] Gastric pH >3.0. [b] No response, subject not included in calculation of average value. [c] Atypical response, subject not included in calculation of average value. [d] Gastric pH nonrecordable after indicated time.

readily detectable. The apparent *in vivo* "failure rate" (14%) encountered in this study was, however, less than the approximately 50% "failure rate" found by other investigators (2) who examined capsules of an earlier design under essentially similar conditions (*i.e.*, unrestrained device in subjects sitting erect).

Considering the amount and composition of the antacid formulations used in this study, an initial rise in gastric pH following ingestion of any of the four preparations may be considered a predictable phenomenon. This applies also to those individuals who may have been subject to gastric hyperacidity at the time of antacid administration. That a pH rise was not detectable in some cases is consistent with the assumption of *in vivo* capsule failure. Transmitter failure in certain cases may have been attributable to location in the stomach, *i.e.*, the device may have lodged in an area of the mucosa whereby contact of the sensor with the gastric contents was prevented or impaired.

Evaluation of the data obtained in those cases where transmission of gastric pH values was confirmed suggests that the duration of the buffering action of antacids cannot be measured reliably by this technique. Approximately 40% of the capsules used in this investigation ceased normal transmission shortly after signaling onset of antacid-induced elevation of gastric pH. In view of the observed rapid increase in the gastric pH of fasted subjects to values which exceeded the capsule range (pH above 7), it is presumed that those capsules were emptied from the stomach together with the gastric contents. Emptying of the stomach is often accelerated by significant elevations in gastric pH (3). The capsule may be retained in the stomach for an arbitrary period by securing one end of a measured length of string to the capsule and the other end to the teeth after swallowing the transmitter. Since attachment of a restraining device would create an artificial situation in which the location of the capsule would be unrelated to retention of antacid in the stomach, it was not employed in this investigation.

The results of this investigation suggest that the *in vivo* performance of the modified Heidelberg telemetric capsule is not completely dependable. It may be considered a convenient and useful device for monitoring changes in gastric pH in the period immediately following administration of antacids whose buffering activity is qualitatively predictable. Duration of antacid-induced buffering effect could not, under the conditions of this study, be accurately ascertained, due possibly to acceleration of gastric emptying and consequent ejection of transmitter from the stomach.

(1) E. W. Packman, unpublished data.
(2) R. Brogle, personal communication, May 1969.
(3) J. M. Marcussen, *Acta Med. Scand.*, **172**, 451(1962).

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Formulation of a Morphine Implantation Pellet Suitable for Tolerance–Physical Dependence Studies in Mice

Keyphrases ☐ Morphine implantation pellet, formulation—tolerance, physical dependence studies ☐ Dependence studies—morphine pellet formulation ☐ Cellulose, microcrystalline—implantation pellets

Sir:

There is considerable current interest in the study of morphine addiction, tolerance, and physical dependence. When using laboratory animals (*e.g.*, mice) for such studies, an essential part of the procedure is

administering the morphine in such a way that the animals receive adequate doses of the drug at frequent enough intervals to reach and maintain the desired levels of tolerance and physical dependence. This can be done by repeated daily injections, but this consumes too much time, both in administering the doses and in the time (weeks) it takes for tolerance and dependence to develop. A more convenient alternate procedure is to implant a pellet of morphine subcutaneously, thus allowing a continual gradual release of the drug. Maggiolo and Huidobro (1) have reported such a technique utilizing a pellet of pure morphine base compressed at high pressure. While this pellet proved useful for their studies, it released drug very slowly (25% of the dose in 8 days and 50% in 16 days).

Way *et al.* (2, 3) produced morphine tolerance and dependence in mice by subcutaneously injecting increasing doses of morphine three times a day for 3 consecutive weeks; but from a time-convenience standpoint, they were interested in using the pellet implantation method. However, with the Maggiolo-Huidobro pellet, the mice developed the desired level of tolerance and dependence too slowly. By using a modified formulation developed by these laboratories, Way *et al.* could induce a high degree of tolerance and physical dependence in 2 or 3 days (the modified pellet released 25–50% of the drug in the first 2 days after implantation). Since the publication of the Way articles, we have received a number of requests for manufacturing details. Therefore, the purpose of this Communication is to provide these formulation details pertaining to the experimental products utilized in the previously published paper emanating from these laboratories. For each tablet:

Morphine, purified powder	0.075 g.
Microcrystalline cellulose (Avicel)	0.075 g.
Fumed silicon dioxide (Cab-O-Sil)	0.00075 g.
Calcium stearate	0.0015 g.

Directions: Screen the morphine, microcrystalline cellulose, fumed silicon dioxide, and calcium stearate through 60-mesh screen. Slug using 1.91-cm. (0.75-in.) FFBE punch and die, obtaining thin, firm wafers. Screen, No. 16 mesh, *via* Stokes oscillating granulator. Mix well in a twin shell blender. Compress *via* Colton tablet press model 330:

Tablet weight	0.152 g.
Tablet hardness	15 Strong-Cobb Units
Tablet thickness	3 mm.

Because of the possibility of particle segregation in the hopper of the tablet press, the slugging step was introduced. This is especially important in view of the small batch sizes produced.

The determining factor in selecting microcrystalline cellulose as the diluent was the desire to control pellet density or hardness. Because morphine is soluble in tissue fluids and cellulose is not, it is reasonable to expect that, after some initial rapid release of the drug, the absorption rate would become constant as soon as the material at the surface of the pellet has dissolved. While it is quite possible that other materials could also give the desired effect, the microcrystalline cellulose was chosen because: (*a*) it is easily compressed to varying degrees of density while providing a physically stable pellet; (*b*) it proved a satisfactory vehicle for providing a reasonably constant absorption rate for the drug; and (*c*) its physical characteristics are such that after 5 days' implantation the pellet remained as a semisolid palpable mass, facilitating easy removal from the animal.

This work suggests that microcrystalline cellulose is a possible vehicle for long-term implantation pellets for human use, provided, of course, it proves to be safe from a toxicity standpoint. Preliminary information suggests that microcrystalline cellulose may be relatively innocuous since implantation of pellets in mice containing no morphine elicited no overt toxic effects. Whether or not the body can adequately eliminate the cellulose from the tissues remains to be seen.

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(2) E. L. Way, H. H. Loh, and F. Shen, *Science*, **162**, 1290(1968).
(3) E. L. Way, H. H. Loh, and F. Shen, *J. Pharmacol. Exp. Ther.*, **167**, 1(1969).

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Rearrangement of Chloramphenicol-3-monosuccinate

Keyphrases ☐ Chloramphenicol-3-monosuccinate—rearrangement ☐ Chromatography, liquid–liquid, thin-layer—separation, analysis ☐ NMR spectroscopy—structure ☐ Optical rotatory dispersion—identity ☐ IR spectrophotometry—structure

Sir:

Investigation of the behavior of aqueous solutions of chloramphenicol-3-monosuccinate (I) indicated that at pH's near neutrality the compound is incapable of independent existence but rather exists as an equilibrium mixture of itself and a different molecular form. This report concerns the isolation and characterization of the rearranged compound. Details of the chemistry of this process will be reported in a subsequent communication.

Components of the equilibrium mixture were separated by reverse phase liquid–liquid chromatography using a fatty acid *N,N'*-dimethylamide[1] on silanized diatomaceous earth[2] as stationary phase and 0.05 *N*

[1] Hallcomid M-18, The C. P. Hall Co., Akron Ohio.
[2] Celite 545, Johns-Manville, New York, N. Y.